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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,899	08/10/2006	Ney Osvaldo Silva Filho	033794/307767	7174

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EXAMINER	
ML, QIUWEN	
ART UNIT	PAPER NUMBER
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,899	FILHO ET AL.	
	Examiner	Art Unit	
	QIUWEN MI	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,9-16 and 19-32* is/are pending in the application.

4a) Of the above claim(s) *11-14 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,9,10,15,16 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment in the reply filed on 4/4/08 is acknowledged. Any rejection that is not reiterated is hereby withdrawn.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/2008 has been entered.

Claims Pending

Claims 3-5, 7-8, 17, and 18 are cancelled. Claims 1, 2, 6, 9-16, and 19-32 are pending. Claims 11-14, and 19-22 are withdrawn as they are directed toward a non-elected invention groups or species. Claims 1, 2, 6, 9-10, 15, 16, and 23-32 are examined on the merits.

Specification/Abstract Objections

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case, Applicant is required to delete "The present invention relates to" on line 1, and "the invention also refers to" on line 5 of the Abstract to be more clear and concise. The first letter of "the" in lines 1 and 5 should be capitalized after the deletion.

Claim Rejection 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of combat or reversion of ventricular fibrillation comprising the administration of an extract from *Trichilia catigua*, does not reasonably provide enablement for the same method comprising the administration of any *Trichilia* species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2)

the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method for the combat or reversion of ventricular fibrillation, comprising the administration of an extract from plant material of the species *Trichilia* sp. to a patient in need thereof.

(2) The state of the prior art:

According to Ramirez et al (Structure, Conformation and absolute configuration of new antifeedant dolabellanes from *Trichilia trifolia*, Tetrahedron (56: 5085-5091, 2000), the genus *Trichilia* consists of about 230 species mainly distributed in lowland tropical America (page 5085, 1st column, 1st paragraph). Up to now, numerous different activities have been reported among different species of *Trichilia*. For instance, *Thrichilia trifolia* has antifeedant effect (Ramirez et al); *Trichilia heudelotti* leaves has antimicrobial activity (Aladesanmi et al, Antimicrobial activity of *Trichilia heudelotti* leaves, Fitoterapia 71: 179-182, 2000); *Trichilia roka* has hepatoprotective activity (Germano et al, Journal of Pharmacy and Pharmacology, 53 (11): 1569-1574, 2001, see Abstract); and *Trichilia catigua* has antioxidant effect (Tang et al, Antioxidant phenylpropanold-substituted Epicatechins from *Trichilia* ca. Journal of Natural Products 70 (12): 2010-2013, 2007, see Abstract).

There are variations among different species in *Tirchilia*. According to Foster et al (Nutritional value of the aril of *Tirchilia cuneata*, a bird-dispersed fruit, Bistropica 15 (1): 26-31, 1983), only 15 species among 59 has at least 10% of protein, and only nine species among 57 species has more than 40% lipid content (see Abstract).

Up to now there is no prior art regarding the treatment of ventricular fibrillation using *Trichilia* species.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on one single species *Trichilia catigua*, whereas the claim encompasses the whole genus which contains at least 230 species.

As described above, the chemical components vary among different species of *Trichilia*, and each species thus has its distinct biological activity. There is no evidence that certain biological activity of one species warrants the same activity of a broad genus.

(5) The breadth of the claims:

The invention is drawn to a method for the combat or reversion of ventricular fibrillation, comprising the administration of an extract from plant material of the species *Trichilia* sp. to a patient in need thereof.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on treating ventricular fibrillation with *Trichilia catigua*, it is unclear as to whether the other 229 species in *Trichilia* has the same effect as *Trichilia catigua*. The working example is only limited to species *Trichilia catigua*.

The specification has not provided guidance with regard to the distribution of the active ingredients among 230 *Trichilia* species, and it is not clear which species will contain the active component, and which one will not.

(8) The quantity of experimentation necessary:

In order to verify the activity of *Trichilia* sp. in treating ventricular fibrillation, Applicant needs to find out the distribution of the other 229 species all over the world, collect the plant species from different countries, prepare plant extracts from different plant parts of each species (leaves, stem, bark, root, fruit etc), test different extracts with animal models, and evaluate the effect on ventricular fibrillation of the whole *Trichilia* genus as instantly claimed, thus one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the whole genus *Trichilia* has the claimed activity. This experimentation to practice the claimed invention using the whole *Trichilia* genus would be undue.

Claim Rejections –35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6, 9-10, 15, 16, and 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andre et al (WO 200296441), in view of Sander et al (US 6,335,039), further in view of Kowey et al (Cardiovascular Research, 17: 106-112, 1982).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 12/4/2007, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

Andre et al teach a method of using 5-50 % m/m or 0.5-5.5% m/v *Trichilia catigua,* 2-30% m/m or 0.1-7.5% m/v *Paullinia cupana,* 0.5-3% m/m or 0.1-2% m/v *Zingiber officinale* (page 4) and a carrier (excipient) as vasodilators (page 2, lines 10-15). Andre et al also teach that the invention can be administered orally in the form of tablets (solid form), solutions (liquid form) etc (page 5, 2nd paragraph).

Andre et al do not teach treating ventricular fibrillation explicitly, neither do they teach the incorporation of *Croton moritibensis* into the composition.

Sander et al teach a method for producing vasodilation using 2-15% muirapuama (the same as *Croton moritibensis*, see the instant application, page 2, lines 10-15), *Trichilia catigua,* and guarana (the same as *Paullinia cupana*, see the instant specification, page 2, 2nd paragraph) (col 4, lines 15-45).

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the

very same purpose ...[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.).

In the instant case, all of the above-listed ingredients were known as vasodilators. Thus, one of ordinary skill in the art would have had a reasonable expectation that the combination of these compounds would have been additively beneficial in vasodilation.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art as vasodilators. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Although the prior art did not specifically disclose the amounts of each constituent as in claims, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations of components because concentration is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art.

Accordingly, the instant claims, in the range of proportions where no unexpected results

are observed, would have been obvious to one of ordinary skill having the above cited references before him.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use *Croton moritibensis* in Sander together with *Trichilia catigua, Paullinia cupana,* and *Zingiber officinale* in Andre et al in inducing vasodilation. Since both Andre et al and Sander yielded beneficial results in inducing vasodialtion in pharmaceutical industry, one of ordinary skill in the art would have been motivated to make the modifications.

As evidenced by Kowey et al teach that vulnerability of ventricular fibrillation is affected by changes in systemic arterial blood pressure. Small doses of a vasodilator drug can abolish the enhanced ventricular vulnerability induced by norepinephrine, and can augment ventricular electrical stability (see Abstract).

Since Kowey et al teach that ventricular fibrillation could be abolished by pretreatment of vasodilators (see Abstract), the combination of *Croton moritibensis* in Sander together with *Trichilia catigua, Paullinia cupana,* and *Zingiber officinale* in Andre et al would induce vasodialtion, which could further abolish ventricular fibrillation. The dosages of *Trichilia catigua, Paullinia cupana, Zingiber officinale* described in Andre et al (page 4, lines 5 to the bottom of the page) and the dosage of *Croton moritibensis* in Sander meet claims 4 and 5. The result-effective adjustment in conventional working parameters (e.g., determining an appropriate amount of the components within the composition) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan, which dependent upon the condition of the patients.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Applicant argues that the discovery that the claimed plant extracts were useful in the treatment of ventricular fibrillation did not represent a selection "from a finite number of predictable solutions", but instead reflects the identification of the claimed plant extracts as having efficacy for a new use (page 8, last paragraph). Applicant further argues that Kowey et al states that it remains to be determined whether other vasodilator drugs possess a similar potential protection against malignant arrhythmia (page 9, 1st paragraph).

It is true that vasodilator encompasses a wide range of structurally distinct compounds. However, since Andre et al and Sander et al teach claimed herbal extracts to be vasodilators, and Kowey teaches that small doses of a vasodilator drug can abolish the enhanced ventricular vulnerability induced by norepinephrine, and can augment ventricular electrical stability, the cited references make the claimed invention obvious. Although some of the vasodilators may fail to show reduction in ventricular fibrillation as pointed out by Applicant, according to the teaching of the references, it is still obvious to try from among the known prior art vasodilators.

Applicant argues that Pontieri et al states that the observed effect of the claimed plant extracts on ventricular fibrillation does not appear to be due to vasodilating effects, but is instead due to clear and evident electrophysiological action on the heart (page 9, 2nd paragraph).

This is not found persuasive. Pontieri et al conclude that "the mechanism of action of herbal extract Catuama still needs to be better investigated, it seems to prolong intraventricular condution and the plateau duration of repolarization on MAP". Therefore, there is no evidence that the claimed herbal extracts exert ventricular fibrillation through mechanisms other than vasodilation, and there is no basis to conclude that the prolonged intraventricular condution and plateau duration of repolarization on MAP is not due to vasodilation.

Applicant's arguments have been fully considered but they are not persuasive, and therefore the rejections in the record are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Qiuwen Mi whose telephone number is 571-272-5984. The examiner can normally be reached on 8 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

QM

/Terry A. McKelvey/

Supervisory Patent Examiner, Art Unit 1655